M E M O R A N D U M **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

From: Ricardo Espinola, Medical Officer, Devices Review Branch, Division of Blood Applications, Office of Blood Research and Review.

Applicant Name: Medion Grifols Diagnostics AG

Date of Submission: September 24, 2012

MDUFMA Goal Date: July 25, 2013

Submission Tracking Number (STN)	Name of Biological Product	Intended Use
BL 103898/5063	Reverse-Cyte® A_1, B 0.8% Reagent Red Blood Cells and Reverse-Cyte® A_1, A_2, B 0.8% Reagent Red Blood Cells.	The Reverse-Cyte® A_1, B 0.8% Reagent Red Blood Cells and Reverse-Cyte® A_1, A_2, B 0.8% Reagent Red Blood Cells are for the confirmation of ABO blood grouping in gel techniques. For use with the DG Gel 8 System.
BL 103898/5063	Search-Cyte® 0.8%, Search-Cyte® Plus 0.8%, Search-Cyte® TCS 0.8% Reagent Red Blood Cells.	The Search-Cyte® 0.8%, Search-Cyte® Plus 0.8%, and Search-Cyte® TCS 0.8% Reagent Red Blood Cells are for detection of unexpected antibodies in gel techniques. For use with the DG Gel 8 System.
BL 103898/5063	Search-Cyte® Pool 0.8%	The Search-Cyte® Pool 0.8% is for detection of unexpected antibodies in gel techniques. For use with the DG Gel 8 System.
BL 103898/5063	Data-Cyte® Plus 0.8% Reagent Red Blood Cells	The Data-Cyte® Plus 0.8% Reagent Red Blood Cells is for identification of unexpected antibodies in gel techniques. For use with the DG Gel 8 System.

Recommended Action: Approval

Signatory Authorities Action:

Office Signatory Authority: Jay Epstein, MD, Director, Office of Blood Research and Review.

☐ *I concur with the summary review*
☐ *I concur with the summary review and include a separate review or addendum to add further analysis*
☐ *I do not concur with the summary review and include a separate review or addendum*

Office Signatory Authority: Mary Malarkey, Director, CBER, Office of Compliance and Biologics Quality

☐ *I concur with the summary review*
☐ *I concur with the summary review and include a separate review or addendum to add further analysis*
☐ *I do not concur with the summary review and include a separate review or addendum*

Material Reviewed in Developing SBRA	**Reviewer Name – Document (s) Date**
Clinical Review	**Ricardo Espinola** **Review Memos: February 19, 2013, June 6, 2013, July 18, 2013**
CMC Product Review	**Ricardo Espinola** **Review Memos: February 19, 2013, June 6, 2013, July 18, 2013**
Labeling Review (APLB)	**Dana Martin** **Review Memos: February 8, 2013, May 17, 2013** **Ricardo Espinola** **Review Memo: June 6, 2013**
Statistical Review	**Tie-Hua Ng** **Review Memo: April 30, 2013** **Paul Hshieh** **Review Memo: April 30, 2013**
CMC Facility Review	**Qiao Bobo** **Review Memo: February 22, 2013**
OCBQ / DBSQC Bioburden Testing Review	**Simlee Kaur** **Review Memo: January 8, 2013**
OCBQ / DBSQC Testing Plan Review	**Catherine Pool** **Review Memo: February 28, 2013**

Introduction

Medion Grifols Diagnostics AG submitted an efficacy supplement to their Biologics License Application (BLA) for 3% Reagent Red Blood Cells (RRBC). This supplement is for the licensure of 0.8% Reagent Red Blood Cells (RRBC) to be used with the DG Gel 8 Cards manufactured by Diagnostics Grifols, S.A. The DG Gel® 8 System is a manual system that uses column agglutination technology to perform compatibility testing. It requires processing and handling by a technologist, the use of support reagents, and Grifols 510(k) cleared instruments (e.g., DG Therm and DG Spin) for interpretation of the test results.

The DG Gel 8 Cards utilize column agglutination technology. The cards consist of a plastic support with 8 microtubes containing gel solution mixed with different antibodies or buffer. The microtubes containing specific antibodies act as a reaction medium where the red blood cell antigen reacts with the specific antibody. The gel column traps agglutinated cells as they pass through the column during the centrifugation of the card. Non-agglutinated red blood cells form a pellet at the bottom of the microtube.

This application includes a clinical study conducted at four sites: Emory University Hospital (EUH) in Atlanta, Georgia, Gulf Coast Regional Blood Center (GCRBC) in Houston, Texas, Indiana Blood Center (IBC) in Indianapolis, Indiana, and New York Blood Center (NYBC) in Long Island, New York and Westchester Hospital in New York.

Grifols Inc. on behalf of their sister company Diagnostics Grifols, S.A. located in Parets del Valles, Barcelona, Spain, submitted data from the clinical study together with a concurrent original BLA.

Background

RRBC products covered in this supplement are: Reverse-Cyte® A1 and B; Reverse-Cyte® A1, A2 and B; Search-Cyte® 0.8%; Search-Cyte® Plus 0.8%; Search-Cyte® TCS 0.8%; Search-Cyte® Pool 0.8%; and Data-Cyte® Plus 0.8% Reagent Red Blood Cells. The red blood cells are suspended in isotonic medium with added ----------(b)(4)---------- preservatives. The products also contain neomycin (0.01%) and chloramphenicol (0.017%), to prevent microbial contamination. The manufacturing processes for 0.8% RRBC products are similar to the manufacturing process for the licensed 3% RRBC products, except that the diluent used to achieve the final concentration of 0.8% is ----------(b)(4)---------- whereas the diluent for the 3% RRBC reagents is the ----(b)(4)----.

Although there is no marketing history for the Medion Reagent Red Blood Cells for use with the DG Gel 8 System, there is marketing history dating back to 1966 for the 3% Reagent Red Blood Cells from Medion Grifols Diagnostics (MGD) manufactured in Duedingen, Switzerland. MGD has marketed RRBC as 0.8% suspensions for use in gel techniques in Europe since 2010 under the CE mark with a homologous product line.

After review of the original submission, FDA requested additional information on November 9, 2012, November 15, 2012, December 18, 2012, and January 15, 2013. The information requested included confirmation of whether the Diluent ---(b)(4)--- used to dilute the red cell sediments to 0.8% has the same composition as the diluent used in the Clinical Study. All responses to the additional request information were adequate.

Manufacturing Summary

All manufacturing and testing of the RRBC products proposed in this license supplement occur at the Duedingen, Switzerland facility.

MGD manufactures the RRBC in 0.8% suspension, deriving red blood cells from the same red cell ---(b)(4)--- for their already-licensed 3% RRBC. The ---(b)(4)--- diluent is purchased from ----------(b)(4)----------. For the manufacture of 0.8% RRBC, the --(b)(4)--- is diluted with --(b)(4)-- buffer to the final concentration. The date of manufacture (DOM) is the day of red blood cell collection by phlebotomy. Each lot of RRBC in 0.8% suspension has a 61-day dating period.

----------(b)(4)----------

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----------(b)(4)----------

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The bar code added to the vial labels is an element of the process controls used on the instruments to automatically process the DG Gel cards and the necessary accompanying reagents, such as Reagent Red Blood Cells. This bar code contains the product identification, lot number and expiration date of the product.

Chemistry, Manufacturing and Controls (CMC)

The current CMC, outlined in the approved BLA for the previous product remain the same with the exception of specific modifications necessary to manufacture and package product for use in the DG Gel 8 System. These changes are the adjustment of the red cell concentration to 0.8% instead of 3%, ----------(b)(4)--------

----------(b)(4)---------- and the use of the Grifols DG Gel 8 System at final release testing of the product.

The date of manufacture (DOM) is the day of red blood cell collection by phlebotomy. If there was more than one phlebotomy, for example, bleed on day 1 and bleed on day 3, the days after the initial collection until freezing are calculated as shelf life days. The stability of the bottled Reagent Red Blood Cells 0.8% products was evaluated to verify the labeled shelf life of 61 days from the day of red cell collection.

MGD performed qualification and validation studies for the Antimicrobial Preservative Effectiveness test of the 0.8% RRBC suspended in ---(b)(4)--- buffer. The Anti-Microbial Effectiveness test was performed using (b)(4) dilutions of conformance lots. MGD states that there are no new contamination issues as a result of these newly proposed products.

----------(b)(4)----------

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Specifications and Test Methods for Final Product

Reverse-Cyte Groups A1 and B **Reagent Red Blood Cells 0.8%±0.1%**	**Test Method**
---(b)(4)--- ---(b)(4)--- ----------(b)(4)----------	(b)(4) (b)(4) ----------(b)(4)-------- ---------- ----------(b)(4)---------- ----------
Reverse-Cyte Groups A1, A2 and B **Reagent Red Blood Cells 0.8%±0.1%**	
----(b)(4)--- ---(b)(4)---- ---(b)(4)---- ----------(b)(4)----------	(b)(4) (b)(4) ---------(b)(4)---------- ------ ---------(b)(4)---------- ------
Search-Cyte **Reagent Red Blood Cells 0.8%±0.1%**	**Test Method**
---(b)(4)--- ----------(b)(4)----------	---------(b)(4)---------- ------

----------(b)(4)---------- ---------- ----------(b)(4)---------- ----------(b)(4)---------- ----------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)----------	---------(b)(4)---------- ------ ---------(b)(4)---------- ------ ---------(b)(4)----------
Search-Cyte Plus **Search-Cyte Pool** **Reagent Red Blood Cells 0.8%±0.1%**	
------(b)(4)-------- ------(b)(4)-------- ---------- ----------(b)(4)---------- ----------(b)(4)---------- ----------(b)(4)---------- ----------(b)(4)---------- ---------(b)(4)----------	---------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)----------
Search-Cyte TCS **Reagent Red Blood Cells 0.8%±0.1%**	
-------(b)(4)-------- -------(b)(4)-------- ----(b)(4)---- ----------(b)(4)---------- ----------(b)(4)----------	---------(b)(4)---------- ---------(b)(4)----------

----------(b)(4)---------- ----------(b)(4)---------- ---------(b)(4)---------- ---------(b)(4)----------	 ---------(b)(4)---------- ---------(b)(4)----------
Data-Cyte Plus **Reagent Red Blood Cells 0.8%±0.1%**	
---------(b)(4)---------- ---------(b)(4)---------- ----------(b)(4)---------- ----------(b)(4)---------- ----(b)(4)------ ----------(b)(4)---------- ----------(b)(4)---------- --------(b)(4)-------- ----------(b)(4)---------- --------(b)(4)---------- ----------(b)(4)---------- ----------(b)(4)---------- ----------(b)(4)---------- ----------(b)(4)----------	---------(b)(4)---------- ---------(b)(4)---------- ----------(b)(4)---------- ----------

Facilities

The facilities used for the manufacture and testing of the 0.8% RRBC are the same as those used for the 3% licensed RRBC, at Medion Grifols Diagnostics AG, Duedingen, Switzerland under FDA license number 1740. The ---(b)(4)--- floor, i.e., the Production Area, includes the following facilities: manufacture material preparation area, manufacture sterile bulks area, aseptic filling area, labeling area, packaging area, (b)(4) storage rooms, a lyophilizer, (b)(4) cold rooms, chemicals storage area, (b)(4) washing areas, autoclave and manufacture unsterile bulks area. The aseptic filling and the manufacture sterile bulks are clean rooms class ----(b)(4)----- including sterile bench class (b)(4). The Storage Area includes a warehouse, cold room, and (b)(4) room temperature storage areas.

Water Systems

There have been no changes to the water system or water quality used to manufacture the newly proposed products.

The System for purified water meets the ----------(b)(4)---------- standards for Purified Water as referenced in --(b)(4)--. The potable water is delivered by the municipality of Düdingen and fulfills the requirements of drinking water according to Swiss cantonal regulations. ---(b)(4)--- is continuously monitored by a --(b)(4)-- tester. Potable water passes through a --(b)(4)--- module and is then used as feed water for ------(b)(4)---- units in a serial setup. The ----------(b)(4)--------- system and the subsequent --------(b)(4)---------- system (b)(4) are used for further purification.

Water from (b)(4) and (b)(4) is monitored to meet the specifications for the conductivity of purified water and is stored in a tank, then delivered with a pump to the distribution loop system. ----------
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----------(b)(4)----------

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HVAC Systems

There have been no changes to the HVAC system or environmental controls used to manufacture the newly proposed products. Air is produced by air conditioning unit and blown in a classified (b)(4) clean room through HEPA filter (b)(4). The filtered air is exhausted to the adjacent room through filters mounted in the wall, creating a positive pressure, and then recirculated in the air conditioning system. The clean rooms meet ----------(b)(4)----------.

Computer Systems

The only additional computer system that will be implemented as a result of this modification is related to the use of the ----------(b)(4)---------- for the determination of the -----(b)(4)-----.

Stability Studies

The expiry for the 0.8% RRBC is 61 days.

Stability was monitored in the Product Testing Team (PTT) laboratory of MGD. The stability studies included temperature cycling study, real time stability, stress testing (transport/shipping study) and repeatability study. Sample aging, anticoagulants and interference substance studies were also performed.

Stability testing included a ---(b)(4)--- testing (----(b)(4)----, the vials were tested for QC specifications), and ----------(b)(4)---------- stability testing), where samples of each cell were kept at 2-8 °C. Each day, the samples were ----------(b)(4)---------- day 59 (day before last stability testing day). This was followed by real time stability testing comprised of ----------(b)(4)---------- throughout the shelf life of the products and then stress testing (Transport study). The stability studies were monitored in the PTT Laboratory of MGD.

The stability criteria included ----------(b)(4)---------- throughout the dating period. All the products, met the stability criteria.

Shipping

The shipping validation study for the 0.8% RRBC from Dudingen, Switzerland to ----------(b)(4)---, U.S. is an extension of existing validation data (Transportation Validation S-11.01/00 and S-11.02/00 for the 3% RRBCs).

The Shipping study was performed on Reverse-Cyte A_1, A_2 B 0.8%, Search-Cyte 0.8% and Data-Cyte Plus 0.8%. The results of the shipping study and stability study were within the acceptance criteria.

Clinical Studies

MGD conducted a clinical study at the following clinical sites: Emory University Hospital (EUH), Indiana Blood Center (IBC), New York Blood Center (NYBC) which included Westchester Medical Center and Long Island Medical Center (WMC/LIC) and Gulf Coast Regional Blood Center (GCR). These studies were conducted using the DG Gel 8 System.

Three sites performed the Reproducibility Studies: NYBC/LIC, IBC, GCR. There were a total of 5040 tests performed among the three sites in the Reproducibility Study. There was some variability in the strength of reactions observed during the course of the testing, but none of these differences exceeded a 2+ difference. The results indicated that there is a 100% agreement for both negative and positive results in all cases.

Three sites performed the Comparison Studies: NYBC (LIC and WMC), IBC, and EUH.
The comparison studies involved three lots of each of the cards and included more than 12,000 data points for the RRBCs [and more than 37,000 Gel Card reagents results.]

1. 3000 ABO reverse grouping tests (3000 x 3 tubes per samples = 9000)
2. 1000 Antibody screening [334 (including 60 pos) per site] (1002 x 2 RRBCs) = 2004
3. 100 Antibody Identification (34 panels x 11 cells/site). (102 x 11 = 1122)

The tables below summarize the results of the clinical study.

Reverse ABO Group (A1 cell)

A1 cell		Comparator EUH		Comparator NYBC		Comparator IBC		Comparator 3 sites pooled	
		Pos.	Neg	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
DG Gel 8	Pos.	614	0	636	0	520	2	1770	2
	Neg.	0	386	2	375	3	498	5	1259
PPA (Lower 95% CB)		100% (99.51%)		99.69% (99.02%)		99.43% (98.52%)		99.72% (99.41%)	
NPA (Lower 95% CB)		100% (99.23%)		100% (99.20%)		99.60% (98.75%)		99.84% (99.50%)	
OPA (Lower 95% CB)		100% (99.70%)		99.80% (99.38%)		99.51% (99.98%)		99.77% (99.57%)	

PPA – Positive Percent Agreement
NPA – Negative Percent Agreement
OPA – Overall Percent Agreement

Reverse ABO Group (A2 cells)

A2 cell		Comparator EUH		Comparator NYBC		Comparator IBC		Comparator 3 sites pooled	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
DG Gel 8	Pos.	601	0	606	2	516	2	1723	4
	Neg.	0	399	15	390	3	502	18	1291
PPA (Lower 95% CB)		100% (99.50%)		97.58% (96.30%)		99.42% (98.51%)		98.97% (98.47%)	
NPA (Lower 95% CB)		100% (99.25%)		99.49% (98.40%)		99.60% (98.76%)		99.69% (99.29%)	
OPA (Lower 95% CB)		100% (99.70%)		98.32% (97.49%)		99.51% (99.98%)		99.28% (98.97%)	

Reverse ABO Group (B cell)

B cell		Comparator EUH		Comparator NYBC		Comparator IBC		Comparator 3 sites pooled	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
DG Gel 8	Pos.	816	0	838	1	844	1	2498	2
	Neg.	0	194	6	166	0	178	6	528
PPA (Lower 95% CB)		100% (99.63%)		99.29% (98.60%)		100% (99.65%)		99.76% (99.53%)	
NPA (Lower 95% CB)		100% (98.39%)		99.40% (97.19%)		99.44% (97.38%)		99.62% (98.82%)	
OPA (Lower 95% CB)		100% (99.70%)		99.31% (98.70%)		99.90% (99.54%)		99.74% (99.52%)	

Reverse ABO Group (Combined A1 and B cells)

Combined A1 and B cell		Comparator EUH		Comparator NYBC		Comparator IBC		Comparator 3 sites pooled	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
DG Gel 8	Pos.	1430	0	1474	1	1364	3	4268	4
	Neg.	0	570	8	541	3	676	11	1787
PPA (Lower 95% CB)		100% (99.79%)		99.46% (99.03%)		99.78% (99.43%)		99.74% (99.57%)	
NPA (Lower 95% CB)		100% (99.48%)		99.82% (99.13%)		99.56% (98.86%)		99.78% (99.49%)	
OPA (Lower 95% CB)		100% (99.85%)		99.56% (99.23%)		99.71% (99.42%)		99.75% (99.62%)	

Antibody Screening (Anti-IgG and Search-Cyte Plus 0.8%)

Antibody Screening (Search-Cyte Plus 0.8%)		Comparator EUH		Comparator NYBC		Comparator IBC		Comparator 3 sites pooled	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
DG Gel 8	Pos.	76	1	84	4	60	0	220	5
	Neg.	0	290	1	429	0	274	1	993
PPA (Lower 95% CB)		100% (96.13%)		98.82% (94.54%)		100% (95.13%)		99.55% (97.87%)	
NPA (Lower 95% CB)		99.66% (98.38%)		99.08% (97.90)		100% (98.91%)		99.50% (98.95%)	
OPA (Lower 95% CB)		99.73% (98.71%)		99.03% (97.98%)		100% (99.11%)		99.51% (99.03%)	

Antibody Identification (Anti-IgG and Data-Cyte Plus 0.8%)

Antibody Identification (Data-Cyte Plus 0.8%)		Comparator EUH		Comparator NYBC		Comparator IBC		Comparator 3 sites pooled	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
DG Gel 8	Pos.	182	0	170	2	168	0	520	2
	Neg.	0	236	20	182	13	193	33	611
PPA (Lower 95% CB)		100% (98.37%)		89.47% (85.07%)		92.82% (88.82%)		94.03% (92.10%)	
NPA (Lower 95% CB)		100% (98.74%)		98.91% (96.62%)		100% (98.46%)		99.67% (98.98%)	
OPA (Lower 95% CB)		100% (99.29%)		94.12% (91.71%)		96.52 (94.53%)		97.00% (96.04%)	

Note: The PPA at NYBC and IBC were below 95% because of differences in enhancement reagents used. A ----------(b)(4)---------- method was used at the NYBC and IBC while a ----------(b)(4)---------- was used at EUH. Both methods are valid but (b)(4), though very sensitive, has a higher rate of false positives compared to (b)(4).

In evaluating all of the discrepancies found during the comparison study, it was noted that of the 56 data points evaluated by the referee laboratory, 73% had the correct result for DG Gel.

Environmental Assessment

MGD requested a categorical exclusion under 21 CFR 25.31 without specifying a subcategory. DMPQ requested MGD to specify the subcategory of their request and to provide a brief justification. The response from MGD was considered acceptable.

Labeling

On May 21, 2013 FDA requested Medion Grifols Diagnostics, Inc. to revise the four package inserts of the products. MGD revised the package inserts as requested. The labeling for these 4 products meets the requirement outlined in 21 CFR 610.60, 21 CFR 610.61, 21 CFR 610.62, 21 CFR 660.35 and 21 CFR 809.10.

Recommendations

Based on the review of the information provided in this submission and the responses to the additional information requested from Medion Grifols Diagnostics, Inc., the review committee recommends approval of this efficacy supplement.